As the HIV pandemic spreads through regions of the world, it takes a particularly discouraging toll on children and young adults—our collective future. Infants and children born to HIV-infected parents face a double threat: if they escape the 25%–40% risk of HIV infection through perinatal and breast-feeding exposure, they remain at high risk for losing one or both parents to the disease. Of the 39.5 million people estimated to be living with AIDS globally as of December 2006, 2.3 million were <15 years old, with ~530,000 youngsters (1500/day) newly infected during the past year [1].

Perhaps the greatest advance in HIV-related public health has been the use of antiretrovirals (ARVs) for the prevention of mother to child transmission (PMTCT). The initial report of the complex use of zidovudine by mother-infant pairs in the landmark AIDS Clinical Trials Group 076 study [2] and the subsequent report of a simple single-dose nevirapine regimen used in HIV Network for Prevention Trial 012 [3], and of many useful variations on these 2 models that followed, have transformed PMTCT practices. Although partnerships between governments and nongovernmental organizations have developed broad PMTCT implementation programs, significant limitations regarding penetration and uptake on a population scale remain to be solved. The result is a constant expansion of the ranks of HIV-infected children with recently infected newborns and young infants.

In parallel with ongoing prevention efforts and while awaiting new developments in areas such as HIV vaccine research, ARV treatment has assumed appropriate urgency. Here, the targeting and inclusion of infected infants and children for treatment has been disappointingly slow. The many reasons for this lag include the high cost and limited availability of appropriate drug formulations, a lack of health care expertise, personnel and infrastructure needs, and a relative absence of advocacy in the prioritization process. In addition, the sheer size of the problem is daunting—the cost combined with lack of infrastructure in most settings of highest need has led some researchers to conclude that the problems are beyond solution.

The article in the present issue of the Journal by George et al. [4], from the Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (Gheskio) program in Port-au-Prince, Haiti, provides us with validation that ARV treatment programs targeting infants and children in low-income settings are both feasible and effective. Haiti has the lowest per-capita income in the Western hemisphere and some of the most challenging sociopolitical and economic conditions in the world. Gheskio can boast an accomplished track record in both provision of care and operational research, having assembled a skilled in-country and international team of specialists addressing multiple medical problems. Do not be mistaken that this comprehensive program—with its team of 3 pediatricians, a nurse, psychologist, pharmacist, and 2 community health workers—represents the standard of care or state of affairs at health-care sites attempting pediatric HIV treatment in low-income settings. Rather, it represents the vanguard of what is possible. One of the team’s aims is to probe options for widespread implementation. Nevertheless, the Gheskio team presents a legitimately hopeful report of what is achievable in very difficult treatment environments.

The Gheskio experience with this pediatric cohort is both informative and representative. Over the course of a 3-year period, 622 HIV-infected children attended the clinic, either through referral from related PMTCT programs or public or private health-care providers or by self-referral. These children presented with a relatively high frequency of severe illness, given that 285 (46%) were started on...
ARVs. The risk for and rate of HIV disease progression and mortality among infants is known to be quite high, relative to that in older children and adults—a phenomenon first observed in US and European pediatric cohorts [5]. Mortality rates among untreated African infants infected with HIV approach 50% by 2 years of age, and these are almost certainly exacerbated by malnutrition and prevalent coinfections [6]. Because very young children often deteriorate rapidly, it is difficult to preselect those most in need of treatment. In this setting, there is a clear logic to early therapeutic intervention that requires timely diagnosis. Infant diagnosis presents another challenge in that it requires direct viral detection, usually by means of a polymerase chain reaction–based assay, which is not widely available in the setting of limited resources.

PMTCT and ARV treatment programs have been developed in different time periods, often under different funding sources and administered by different agencies. This has frequently resulted in stand-alone programs with less than ideal linkages within the same geographic region. In addition, long-standing national tuberculosis (TB) treatment programs, often with substantial infrastructure, are not effectively linked with the newer HIV-related programs, despite the fact that HIV–associated TB is an all too common occurrence. Better coordination of HIV and TB care and prevention services among government programs, funding agencies, and their implementing partners are needed to improve uptake and quality of care with subsequent improved patient outcomes.

As evidenced by the GHESKIO cohort, the diagnosis of TB in children is exceedingly challenging, with the majority being classified as “probable” or “suspect” on the basis of assessments of a combination of clinical signs and symptoms, TB skin-test results, and radiographic findings. Treatment of children with HIV-associated TB is equally problematic, especially considering that nevirapine, which is a mainstay of infant HIV therapeutics in low-income countries, is not recommended for pharmacokinetic reasons when rifampin-based regimens are being used to treat TB. Some clinicians have attempted to use increased nevirapine dosing or to substitute efavirenz (for which dosing in children <3 years old has not yet been established) when treatment of HIV and TB is needed, but the options are far less than ideal. Thirty of the original 285 children treated in the GHESKIO program were placed on suboptimal 2-drug ARV regimens because of concomitant TB treatment. Consequently, these 30 children were excluded from the analyzed cohort of 236 children treated with 3-drug ARV regimens. An additional 48 children in the formal cohort were also treated for TB at some point, resulting in 78 (27%) of the original 285 children treated for HIV also having a diagnosis of and being treated for TB. The authors note the high mortality associated with a TB diagnosis in their cohort (9/21 deaths). Although George et al. chose not to include TB in the Cox analysis because most of these were clinical diagnoses, without better TB diagnostics, we are unlikely to produce more reliable data on this issue in the near future.

Although the criteria for inclusion into the analysis cohort required that HIV therapy be indicated by current World Health Organization (WHO) criteria, in general children presented with highly advanced disease: 58% were classified as having WHO clinical stage 4, and the median CD4+ T cell percentage was 12%. This phenomenon has been observed in many settings where ARVs are initially being offered and is associated with a high early mortality rate, regardless of the institution of therapy. The majority of deaths in the GHESKIO cohort occurred within the first 6 months, with a median interval of 48 days. In fact, the authors report that a “number” of children died before therapy could be started, during the median 10-week period between enrollment and the initiation of ARV therapy. These observations, together with the dramatically improved survival rates noted among infants started on therapy, support the need for improved coordination between PMTCT and ARV treatment programs, to promote the swift identification of children at risk, earlier diagnosis, and prompt initiation of ARV therapy.

Given the rapid disease progression during infancy mentioned above and the median GHESKIO cohort age of 6.3 years, this cohort by and large represents “survivors.” As George et al. acknowledge, survivor selection bias most certainly affected some of the statistical outcomes. However, the low mortality rate and the gratifying improvements documented for both CD4+ T cell percentages and weight support a dramatic treatment response. Although a 56% nondetectable viral RNA rate after 12 months of therapy is reasonable, it suggests underlying problems with nonadherence, ARV potency, or both, which are commonly observed issues in pediatric therapeutics everywhere. Given the use of single-dose nevirapine for PMTCT and the concomitant reliance on nonnucleotide reverse-transcriptase inhibitors (NNRTIs) for therapy, NNRTI resistance is a significant unknown variable in the outcome analyses. This again echoes the need for program coordination, as well as the need for research about the emergence of resistance and treatment alternatives.

The GHESKIO pediatric cohort experience reported here by George et al., as well as that of others reported elsewhere, firmly supports the feasibility of pediatric HIV treatment in low-resource settings. Rollout and expansion programs to reach wider segments of affected populations will meet with additional, substantial challenges—coordination of resources and programs, sustainability, and increases in funding support among them. Innovative solutions to health care infrastructure and personnel shortages will need to be developed. Operational research must be a cornerstone of future success, and it is expected that the GHESKIO program will continue to help lead the way. There has been an encouraging recognition of and
movement toward scaling up pediatric HIV treatment efforts in low-resource settings, but it bears repeating: the time for treating the children is (and has been) now.

References